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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,321	04/12/2004	Andre Rosowsky	56369 (70157)	5857

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/824,321	ROSOWSKY ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) *1-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/12/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group II, claims 38-55, in the reply filed on 8/1/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter.

Claims 38-55 are under consideration.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on 4/12/2004, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 38, 40 and 44-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Any claim not specifically rejected is rejected as it is a dependent on a rejected claim and share the same indefiniteness.

1. Claim 38 is indefinite for more than one reason. First of all, claim 38 recites a label R for which there is no definition. Hence, it is not clear what is included or excluded in the label R. Secondly, claim 38, which is a process claim, recites

"under conditions conducive to the formation" of C-C bond or compound, and this renders the claim indefinite. One trained in the art has to guess what these conditions are to practice this process. In addition, arriving at the right experimental conditions by one trained in the art in such case cannot be deemed as instant process.

2. Claim 40 is indefinite as it recites, "wherein the compound is a lipophilic inhibitor of dihydrofolate reductase". As recited, it appears that one need to experiment and find such a compound from the genus of claim 39. In addition, a compound is a compound irrespective of its functional attributes. A compound is defined clearly by its structural make-up and difference between two compounds for prior art purpose is based on the structure. See Intirtool, LTD. V. Texar Corp., 70 USPQ2D 1780. Note court held that " In general, a claim preamble is limiting if recites essential structure or steps or if it is necessary to give" life, meaning, and vitality to claim.'.... However, if the body of the claim describes a structurally complete invention such that deletion of the preamble phrase does not effect the structure or steps of the claimed invention,' the preamble is generally not limiting unless there is clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art.""

Instant claim is a compound claim and is clearly defined by a structure namely a bicyclopyrimidine core with specific substituents. Omission of the attributes to the compound of genus of claim 40 would not alter the structure of the compound.

Hence, claims 40 is a duplicate of claim 39.

3. Claim 44 is indefinite as it recites " a compound or composition of claim 39". Note claim 39 is a compound claim not a composition claim.

4. Recitation of "mammal" in claim 46 and claim 52, renders these claims vague and unclear as the disease or disorder appears to be limited to human not to all mammal. For example HIV relates to human and not all mammal.

5. Claim 50 recites "Pneumocystis carinii (Pc)", as parasites but these are fungus not parasites. Also there appears to be a typographical error in spelling Toxoplasma.

6. Claim 51 recites "immuno-comprised", which is typographical error.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 38 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compound of formula I wherein the RZnY is RCH_2ZnY and the R group has no halogen substituents, does not reasonably provide enablement for compound of formula I wherein the RZnY has nay or all R groups and R is variously substituted with functional groups including halogen, which are susceptible to the formation of organozinc compound RZnY formation and as well as self cross coupling.. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following apply:

In evaluating the enablement question, following factors are considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. The nature of the invention and the state of the prior art:

The invention is drawn to a process of cross coupling of aryl halide with organozinc compound in the presence of palladium catalyst followed by condensation with chloroformamidine to make the compound of formula I Specification is not adequately enabled as to how to make compounds of formula (I) wherein the said RZnY lacks a CH_2 in between R and Zn as well as where R is variously substituted with reactive functional groups including halogens which are either susceptible to organozinc compound formation n and self cross coupling..

Instant R as recited is undefined and therefore includes any or all R groups that may not even have a CH_2 interposed between R and Zn to arrive at the compound of formula I. Hence, use of any or RZnY would not result in the compound of formula one. Specification has no support for the making compound of formula I other than using compound of formula Iii shown in the specification. Even , if the R group is clearly defined phenyl and a CH_2 is interposed between R and Zn, instant R_A substituents choices on the aryl ring has many reactive groups that would preclude organozinc or RZnY formation. For example, amino groups would react or interfere

with organozinc compound formation . In addition, presence of halogen such chloro would also either form a unwanted organo zinc halide formation or undergo self cross coupling as evident from the reactivity of such groups shown in the specification. Specification offers no teachings or suggestion as to how to perform the process in presence of these reactive groups. See references cited in the IDS and instant specification. . Thus presence of such reactive groups are chemically incompatible the process of organozinc compound RZnY formation and its subsequent cross coupling reaction embraced in the instant claims.

2. The predictability or lack thereof in the art:

Hence the process as applied to the above-mentioned compounds claimed by the applicant is not an art-recognized process and hence there should be adequate enabling disclosure in the specification with working example(s).

3. The amount of direction or guidance present:

Examples illustrated in the experimental section or written description offer no guidance or teachings as to how perform the process of making compound of formula I when reactive substituents or chemically incompatible substituents are present in the starting material.

5. The presence or absence of working examples:

Although examples in specification show the instant process, they are limited to R-CH_2Zn-Y and those with no reactive functionality. There are no representative examples showing the viability of the process for plurality of reactive substituents embraced in the instant claims.

6. The breadth of the claims:

Specification has no support, as noted above, for all compounds generically embraced in the claim language would lead to desired compound of formula I with said reactive groups and there is also no valid chemical reasoning for one trained in the art to expect that all these functional groups would be inert toward the cross coupling reaction with organozinc reagent or the formation of organozinc reagent itself embraced in the process claim.

7. The quantity of experimentation needed:

The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired structure, namely compound of formula I embraced in the instant claims in view of the reasons outlined above..
Thus, factors such as "sufficient working examples", the "level of skill in the art and predictability, etc. have been demonstrated to be sufficiently lacking in the case for the instant claims.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is

clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claims 44-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pneumonia caused by Pneumocystis carinii infection, does not reasonably provide enablement for treating any or all parasitic infection or disorder in mammals including treating any or all immuno-compromised mammal and those with any or all autoimmune disorder generically embraced in claim 44 including those specifically recited in claims 45-55. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Following reasons apply.

The instant claim 44 and its dependent claims 45-55 are drawn to "treating a mammal suffering or susceptible to parasitic infection or disorder" while the scope claim 45-55 are drawn to treating immuno-compromised mammal with or without autoimmune disorder. The scope of the claims includes not only treating any or all parasitic infections in mammals in general and in any or all immuno-compromised mammal with or without autoimmune disorder for which there is no enabling disclosure. Specification provides no enabling disclosure showing that all parasitic infections or disorders can be treated with the use of the instant compounds. The scope of these claims is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 1-2. The instant compounds are disclosed to have inhibition of DHFR activity and it is recited that the instant compounds are therefore useful in treating any or all

parasitic infections or disorders in mammals and immuno-compromised mammal with or without autoimmune disorder for which applicants provide no competent evidence. Applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for treating any or all parasitic infection and any or all immune disorder disclosed and embraced by the claim language. Prior art search in the related area does not substantiate such a broad scope.

Moreover many if not most of parasitic or bacterial infections such as meningitis, anthrax etc. are very difficult to treat and at present there is no known drug, which can successfully be used to treat infectious diseases. Furthermore, all immune compromised mammals are not susceptible infection. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1090-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method of preventing solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Snyder et al., J. Med. Liban 48(4): 208-214, 2000 (PubMed Abstract provided), wherein with regards to antibacterial therapies, it is stated that " common bacteria whose susceptibility to antimicrobials is no longer

predictable". Note also that despite the fact there are several commercial antibacterial agents are available, it is still difficult to treat several pathogens such as those cause leprosy, meningitis, sexually transmitted infections, anthrax etc.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating parasitic infections that require DHFR inhibiting activity of instant compound.

2) The state of the prior art: Although there are large number DHFR inhibiting agents, none of them are claimed or shown to be useful in treating any or all parasitic infections.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds for treating any or all parasitic infections. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples for treating any or all

parasitic infections. In fact, specification has no testing of any of the compounds of the instant claim 39 and the state of the art is that the effects of bacterial agents based on the disclosed inhibitory activity are unpredictable and at best limited to treating bacterial infections.

6) The breadth of the claims: The instant claims embrace any or all parasitic infections including those yet to be related to DHFR activity.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating variety of parasitic infections and autoimmune disorders of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright,

999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 39-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Broughton et al. Antimicrobial Agents and Chemotherapy, 1348-1355, 1991.

Broughton et al. teaches several 2,4-amino-pyrimidines, which include a compound claimed in the instant invention for treating Pneumocystis carinii infections. See entire document, especially see Table 8, and compound 351521.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Acting Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

10/14/2005